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Original article

Sufficient levels of 25-hydroxyvitamin D and protein intake required to increase muscle mass in sarcopenic older adults – The PROVIDE study

Sjors Verlaan [a, b, *], Andrea B. Maier [c, d], Jürgen M. Bauer [e], Ivan Bautmans [f], Kirsten Brandt [g], Lorenzo M. Donini [h], Marcello Maggio [i], Marion E.T. McMurdo [j], Tony Mets [f], Chris Seal [g], Sander L.J. Wijers [a], Cornel Sieber [k], Yves Boirie [l, m], Tommy Cederholm [n]

[a] Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, The Netherlands
[b] Department of Internal Medicine, Section of Gerontology and Geriatrics, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Human Movement Sciences, MOVE Research Institute Amsterdam, VU University, Amsterdam, The Netherlands
[d] Department of Medicine and Aged Care, Royal Melbourne Hospital, University of Melbourne, Australia
[e] Department of Geriatric Medicine, Carl von Ossietzky University, Oldenburg, Germany
[f] Frailty in Ageing Research Group (FRIA), Vrije Universiteit Brussel (VUB), Brussels, Belgium
[g] Human Nutrition Research Centre, School of Agriculture, Food and Rural Development, Newcastle University Institute for Ageing, Newcastle University, Newcastle upon Tyne, United Kingdom
[h] Department of Experimental Medicine, Section of Medical Pathophysiology, Endocrinology and Human Nutrition, "Sapienza" University of Rome, Italy
[i] Department of Clinical and Experimental Medicine, Section of Geriatrics, University of Parma, Italy
[j] Ageing and Health, Ninewells Hospital and Medical School, University of Dundee, United Kingdom
[k] Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany
[l] CHU Clermont-Ferrand, Service de Nutrition Clinique, F-63003 Clermont-Ferrand, France
[m] Clermont Université, Université d'Auvergne, Unité de Nutrition Humaine, BP 10448, F-63000 Clermont-Ferrand, France
[n] Department of Public Health and Caring Sciences/Clinical Nutrition and Metabolism, Department of Geriatric Medicine, Uppsala University Hospital, Sweden

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SUMMARY

Background: Inadequate nutritional intake and altered response of aging muscles to anabolic stimuli from nutrients contribute to the development of sarcopenia. Nutritional interventions show inconsistent results in sarcopenic older adults, which might be influenced by their basal nutritional status.
Objective: To test if baseline serum 25-hydroxyvitamin D (25(OH)D) concentrations and dietary protein intake influenced changes in muscle mass and function in older adults who received nutritional intervention.
Methods and design: Post-hoc analysis was performed in the PROVIDE study that was a randomized controlled, double blind trial among 380 sarcopenic older adults. This study showed that those who received a vitamin D and leucine-enriched whey protein medical nutrition drink for 13 weeks gained more appendicular muscle mass (aMM), and improved lower-extremity function as assessed by the chair stand test compared with controls. To define low and high groups, a baseline serum concentration of 50 nmol/L 25(OH)D and baseline dietary protein intake of 1.0 g/kg/d were used as cut offs.
Results: At baseline, participants with lower 25(OH)D concentrations showed lower muscle mass, strength and function compared with participants with a high 25(OH)D, while the group with lower protein intake (g/kg/day) had more muscle mass at baseline compared with the participants with higher protein intake. Participants with higher baseline 25(OH)D concentrations and dietary protein intake had, independent of other determinants, greater gain in appendicular muscle mass, skeletal muscle index (aMM/h^2), and relative appendicular muscle mass (aMM/body weight × 100%) in response to the

Abbreviations: 25(OH)D, Serum 25-hydroxyvitamin D; aMM, Appendicular Muscle Mass; BW, Body weight; GDS, Geriatric Depression Scale; MNA-SF, Mini Nutritional Assessment-Short Form (MNA-SF®); MMSE, Mini Mental State Examination; PASE, Physical Activity Scale for the Elderly; SMI, Skeletal Muscle Mass Index (appendicular muscle mass /height^2); SPPB, Short Physical Performance Battery.

* Corresponding author. Nutricia Research, Nutricia Advanced Medical Nutrition, Uppsalalaan 12, 3584 CT Utrecht, The Netherlands.
E-mail address: Sjors.verlaan@nutricia.com (S. Verlaan).

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nutritional intervention. There was no effect modification of baseline 25(OH)D status or protein intake on change in chair-stand test.

Conclusions: Sufficient baseline levels of 25(OH)D and protein intake may be required to increase muscle mass as a result of intervention with a vitamin D and protein supplement in sarcopenic older adults. This suggests that current cut-offs in the recommendations for vitamin D and protein intake could be considered the "minimum" for adults with sarcopenia to respond adequately to nutrition strategies aimed at attenuating muscle loss.

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1. Introduction

Sarcopenia, the geriatric syndrome characterized by low muscle mass, strength, and function, will become increasingly prevalent as the global population ages. This syndrome places considerable stress on health care systems since it is implicated with impaired outcomes in chronic disease [1], as well as higher rates of hospitalization and nursing home admissions [2]. Inadequate nutritional intake and altered response of aging muscles to anabolic stimuli from meals contribute to the multifactorial pathogenesis of sarcopenia. In particular, inadequate intake of high quality protein including essential amino acids such as leucine and low 25-hydroxyvitamin D (25(OH)D) serum levels in older adults are potentially modifiable risk factors for sarcopenia [3–5].

Recent long-term nutrition intervention studies aimed at improving muscle mass, strength and function, however, have shown inconsistent results in sarcopenic and frail older adults [6,7]. The composition of the nutritional supplements, the amount and source of protein and amino acids, fat, carbohydrates and micronutrients such as vitamin D varied among the interventions. Moreover, variations in the health condition of the study populations, presence of multimorbidity, physical activity level, and nutritional status may have influenced the outcomes.

As a result of these heterogeneous findings, we hypothesized that baseline nutritional status could influence the efficacy of vitamin D and protein interventions. To test this hypothesis, we used the data from the PROVIDE study, in which sarcopenic older adults were randomized to either a vitamin D and leucine-enriched whey protein supplement or isocaloric control [8].

2. Materials and methods

2.1. Study design and participants

The PROVIDE study was a 13-week, multi-center, randomized, controlled, double blind, two parallel-group study among older adults with sarcopenia. Detailed information of the trial (registered under the Dutch trials register with the identifier NTR2329) has been published previously [8]. In brief, community-dwelling adults over 65 years were recruited from 18 study centers in Europe, and were eligible when presenting mild to moderate limitations in physical function (Short Physical Performance Battery (SPPB) score 4–9), and low skeletal muscle mass (≤37% (men) and ≤28% (women)) using bioelectric impedance analysis (BIA 101 Akern, Florence, Italy). Those who received the vitamin D and leucine-enriched whey protein medical nutrition drink gained more appendicular muscle mass (aMM), and improved lower-extremity function as assessed by the chair stand test, compared with controls (8).

Participants were randomized to receive either the intervention or an iso-caloric control product twice daily. The intervention product contained per serving 20 g whey protein, 3 g total leucine, 9 g carbohydrates, 3 g fat, 800 IU vitamin D and a mixture of vitamins, minerals and fibers, and the iso-caloric control drink contained only carbohydrates, fat and some trace elements.

Blinded and trained research staff collected information about the baseline characteristics via a questionnaire and assessed the outcomes during the study visits week 7 and 13. Self-reported amount of physical activity was assessed using the European version of the Physical Activity Scale for the Elderly (PASE). Health-related quality of life was determined using the EQ-5D, both as an index (0–1) and as a visual analogue scale (0–100). Cognitive function was measured using the Mini Mental State Examination (MMSE, 0–30) and cognitive impairment; i.e., MMSE <25 was an exclusion criterion. The Geriatric Depression Scale (GDS, 0–15 points) was used to assess potential depression symptoms. Finally, the Mini Nutritional Assessment-Short Form (MNA-SF®) was used to evaluate participants' nutritional status. The total score of the six questions (0–14 points) indicated whether the participant was well-nourished (12–14 points), at risk for malnutrition (8–11 points) or malnourished (0–7 points).

2.2. Muscle related outcomes

Appendicular muscle mass (aMM) was measured at baseline and week 13 using Dual energy x-ray absorptiometry (DXA, different models from Hologic, Bedford, USA; and Lunar, Fairfield, USA). Raw DXA data were centrally analyzed at the Vrije Universiteit Brussel, Brussels, Belgium, using a standardized protocol by the same researcher. Analyses were performed with and without correction for height^2 (skeletal muscle mass index, SMI: aMM/h^2) [9] or body weight (relative appendicular muscle mass: aMM/BW × 100%) [10].

The chair stand test measures the time required to rise five times from a chair without arm rests. It is one of the three components of the SPPB, along with gait speed and balance tests [2]. Maximum handgrip strength was calculated by taking the average of the highest measurement of two consecutive measures in each hand by using a hydraulic hand dynamometer (Jamar™, Preston, Jackson, Missouri, USA).

2.3. Serum 25-hydroxyvitamin D analysis

Analysis of serum 25(OH)D was performed at Reinier de Graaf Groep medical laboratory, Delft, the Netherlands using chemiluminescense micro-particulate immunoassay (Abbott Laboratories, Wiesbaden, Germany). The recovery of endogenous 25(OH)D both D3 and D2 species were 105% and 85%, respectively compared with a chromatography-based reference method. Serum 25(OH)D concentration was used as a dichotomous variable for most analyses with a cut-off of 50 nmol/L, which was similar to generally accepted threshold of serum 25(OH)D deficiency in older adults [11–13].

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